PLASMA ATHEROGENIC INDEX IS AN INDEPENDENT INDICATOR AND PROGNOSTIC VALUE IN RAYNAUD'S PHENOMENON?

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Abstract

Objective: Raynaud's phenomenon (RP) is characterized by cold induced temporary ischaemia of the fingers or toes and an inflammatory autoimmune disease of connective tissues. Plasma atherogenic index (PAI) is a valuable marker for the cardiovascular disease and cardiac risk. The aim of this study was to evaluate the role and clinical use of PAI in RP patients.

Materials and Methods: In this retrospective-cohort study, we examined the clinical value count blood cells in 55 patients with RP and 14 clinical controls admitted Konya Training and Research Hospital Department of Cardiovascular Surgery between January 2016-March 2019 were investigated retrospectively screened. PAI was measured as a logarithmic value of triglyceride to high-density cholesterol ratio. PAI levels <0.11 is accepted as low risk, 0.11-0.21 intermediate risk, and 0.21 >increased risk. PAI was measured as a logarithmic value of triglyceride to high-density cholesterol ratio. The lipid and other biochemical parameters of patient and control groups were examined and measured.

Results: The study consisted of 29 females (42.03%) and 40 males (57.97%). There was a significant difference between differences between PAI level groups. There was no significant difference in PAI results between genders ($p>0.355$). We also found disagreement in biochemical parameters and PAI between controls and patients.

Conclusion: When we evaluated PAI in the patients with RP and controls, it was determined that there was no significant difference in either parameter. However, PAI levels have showed that significant elevated between groups so it can be a simple, economic and non invasive marker to identify for future studies.

Keywords: Raynaud's phenomenon, Plasma atherogenic index, Blood lipid components

Introduction

Raynaud's phenomenon (RP) as an episodic, symmetrical, vasospastic disorder resulting in classic triphasic colour change, trophic changes limited to the skin and uncomfortable sensory symptoms of the extremities in the absence of arterial occlusion described by, Maurice Raynaud In the 19th century first (1). The pathophysiology of RP remains uncertain. Raynaud's disease was divided into primary and secondary Raynaud's phenomenon. Systemic and local vascular effects were most likely to be involved in primary Raynaud's disease, whereas additional abnormalities in vascular structure and vascular function are suggested to cause secondary Raynaud's phenomenon. (2).

Plasma atherogenic index (PAI) is expressed as the base 10 logarithm of the ratio of the concentration of triglyceride (TG) to high density lipoprotein cholesterol (HDL-C), where each concentration is

expressed in mmol/L. This quantity has been shown to reflect the distribution of particle sizes in lipoprotein subclasses and correlates significantly with the presence of risk factors for atherosclerosis such as gender, age, dyslipidemia and diabetes as well as positive findings on cardiovascular disease and cardiac risk. PAI has three risk categories low < 0.11, intermediate: 0.11–0.21 and high >0.21 (3,4). There are no studies investigating the relationship between PAI level and RP in the literature. We aimed of this study was to evaluate the role and clinical use of PAI levels in RP patients.

Materials and Methods

This study was a retrospective case series comparing a patient group with RP and a control group consisting of healthy subjects. 55 patients with RP and 14 clinical controls, admitted Konya Training and Research Hospital Department of Cardiovascular Surgery between January 2016-March 2019 were

investigated retrospectively screened. Patients with polyneuropathy, hormone replacement and antiplatelet therapy, amyotrophic lateral sclerosis, multiple myeloma, multiple sclerosis, Parkinson's disease, poliomyelitis, diabetes mellitus, uremia, amyloidosis, cancer, congestive heart failure, Cushing's syndrome, hypo- or hyperthyroidism, pregnancy, lactation, chronic kidney failure, neuroleptic or antidepressant usage, cigarette smoking, steroid treatment (for whatever reason), systemic inflammatory diseases, and hematologic diseases were excluded. The study was approved by the local ethics committee.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 21.0 software (IBM Corp, Armonk, NY, USA). Summary statistics of the study population were expressed as the mean $\pm$ standard deviation (mean $\pm$ SD) or median value with the interquartile range (IQR), as appropriate. Comparisons of demographic and clinical parameters of the two groups were performed using the Chi-square test, Student t-test

(independent samples t-test), ANOVA, or Mann-Whitney U-test, as appropriate; the Kruskal-Wallis test was used for the comparison of more than two groups. Sensitivity and specificity were calculated with 95% confidence interval and presented as a table. All p-values of less than 0.05 based on a two-tailed test were considered statistically significant.

Results

A total of 55 RP patients and 14 healthy control were included retrospectively in the present study. The characteristics of biochemical parameters the participants in the two groups are summarized in **Table 1**. Of the patients with RP, of 29 females (42.03%) and 40 males (57.97%). The Plasma Atherogenic Index data are shown in **Table 2**. There was a significant difference between differences between PAI level groups ($p < 0.000$). **Table 3**. has shown that the Plasma Atherogenic Index Levels According to Genders and RP patients group and control groups. There was no no significant difference in PAI results between genders and groups respectively ($p > 0.355$, $p > 0.875$).

Table 2: The Plasma Atherogenic Index Level

	N	%95 CI(Lower-Upper)	median	Min-Max	P
PAI<0,11 low risk	13	-0,04-0,06	7,52	-0,17-0,11	0,000
PAI (0.11- 0.21) intermediate risk	8	0,07-0,23	5,03	0,04-0,36	0,000
PAI>0,21 increased risk	48	0,43-0,56	14,10	0,21-1,13	0,000
Total	69	0,30-0,43	42,55	-0,17-1,13	0,000

PAI: Plasma Atherogenic Index

Table 3: The Plasma Atherogenic Index Levels According to Genders and Groups

	N	Mean	p
Raynoud Patients	55	0,37	0,875
Controls	14	0,36	
Males	40	0,34	0,355
Females	29	0,4	

Table 1: Comparison of biochemical parameters in patient groups and healthy controls

	RP Group Mean	%95 CI (Lower-Upper)	median	Min-Max	Control Group Mean	%95 CI (Lower-Upper)	median	Min-Max	P
Glu	90,86	86,79-94,94	87,5	58-217	92,88	85,83-99,93	90	73-141	0,137
URE	25,18	23,70-26,60	24	8-42	28,70	25,60-31,80	28	19-42	0,137
CREA	0,80	0,77-0,82	0,80	0,48-1,11	0,82	0,76-0,89	0,80	0,72-1,04	0,494
GFR	111,23	108,58-111,88	112,9	78,6-136	109,72	100,79-118,63	110,5	78-135	0,742
UA	4,77	4,44-5,10	4,40	2,80-8,60	5,12	3,94-5,19	5,30	2,60-6,50	0,21

TP	6,78	5,77-7,78	7,40	0,8-7,90	25,40	32,62-83,42	7,35	6,80-80,10	1
ALB	6,32	3,74-8,91	4,55	3,50-48,20	4,46	4,14-4,78	4,48	4,10-4,83	0,652
TBIL	0,89	0,52-1,26	0,60	0,20-8	0,7	0,27-1,21	0,80	0,3-1,10	1
DBIL	0,16	0,11-0,21	0,13	0,04-1	2,46	-3,47-8,39	0,16	0,05-14	0,243
AST	22,80	20,94-24,66	21	13-93	23,82	20,26-27,38	21	16-42	0,407
ALT	19,07	16,38-21,75	14	7-99	18,76	14,80-22,72	18	9-36	0,246
ALP	80,44	66,10-94,78	70	26-281	82,21	66,10-94,78	71	26-281	0,718
GGT	22,18	8,42-35,93	14	7,50-264	23,14	8,42-35,93	15	7,50-264	0,526
LDH	227,93	205,19-250,67	216	2,37-419	248,5	170,18-326,81	217	182-351	0,652
CHOL	174,85	164,17-185,54	174	76-303	170,28	150,60-189,97	171	98-232	0,862
TRIG	114,52	98,79-130,25	97	45-352	162,07	100,42-223,71	134	53-416	0,179
HDL	48,16	44,93-51,38	46	30-93	45,21	38,10-52,32	46	28-68	0,481
LDL	104,45	95,83-113,06	103	31-194	95,5	78,48-112,51	95,5	53-162	0,314
CA	9,48	9,38-9,59	9,50	7,8-10,6	9,54	9,26-9,81	9,50	9,20-10	0,821
NA	137,97	137,97-138,64	138	124-143	138,5	137,41-139,58	138	136-143	0,946
K	4,34	4,25-4,43	4,28	3,55-5,24	4,37	4,23-4,51	4,38	4,02-4,84	0,536
FE	278,14	253,19-303,10	266	16-201	87,75	-17,58-193,08	81,5	19-169	0,771
CRP	37,21	-24,15-98,57	3,14	3,02-3002	19,82	-26,25-65,89	3,13	3,03-86,20	0,791
RF	11,07	10,84-11,31	11,30	9,13-15,70	10,48	8,54-12,41	10,4	9,75-11,30	0,173
SEDIM	6,82	5,24-8,39	3	1-30	7	-8,11-22,11	4	3-14	0,172

Glu:glucose, Crea: creatinine, GFR:glomerul filtration rate, UA:uric acid, TP: total protein, ALB:albumin, TBIL: total bilirubin, DBIL: direct bilirubin, AST: aspartate aminotransferase, ALT:Alanine transaminase, GGT: Gamma-glutamyltransferase, LDH: Lactate dehydrogenase, CHOL: cholesterol, TRIG: triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CA: calcium, NA: sodium, K: potassium, FE: iron,CRP: C-reactive protein, RF: rheumatoid factor, SEDIM: sedimentation

Discussion

Raynaud's phenomenon is a common clinical disorder which affects up to ten per cent of the population (5–7). The clinical appearance of Raynaud's phenomenon is categorized by cold induced temporary ischaemia of the fingers or toes (8,9). In primary Raynaud's phenomenon, no underlying disease can be found, while in secondary Raynaud's phenomenon, a causative local or systemic disorder is present (10).

Plasma Atherogenic index (PAI) is a novel index composed of triglycerides and high-density lipoprotein (11). It has been used to quantify blood lipid levels and commonly used as appropriate

indicator of dyslipidemia and associated diseases (e.g., cardiovascular diseases) (12–14). PAI, calculated as $\log_{10}(\text{TG}/\text{HDL-C})$, was initially constructed as a biomarker of plasma atherosclerosis (11) and has been proved to be notably correlated with other substantial atherosclerosis indexes such as LDL-C size and small-dense LDL-C (15,16). There have been several studies have detected an association between PAI and atherosclerosis-related conditions. For example, Abdullah and his friends and Cure and his friends have demonstrated that PAI was considerably and positively correlated with carotid intima-media thicknesses ($r = 0.304$, $P < 0.001$; $r = 0.261$, $P < 0.001$) (17,18). Dobiášová et al. (4) demonstrated that AIP inversely correlates with LDL-C particle size in a high diversity population composed of both high and low-risk individuals with high correlation. In Maia et al.'s study, there were notably higher values for the PAI in patients with ankylosing spondylitis(AS) than in the healthy control subjects (19). Cure and friends have found PAI values of the patients with AS were higher than those of the healthy control subjects, the LDL levels and TC/HDL ratio were the same in both group (20). Onat and his friends (21) after a 7.8-year follow-up of 2676 middle-aged adults showed that PAI is a reliable biomarker for predicting CVD morbidity. To

support the theory that PAI predicts the risk of development of type 2 diabetes mellitus better than traditional lipid markers, a meta-analysis of 15 studies was done (22). Similar results of PAI as useful tool for the diagnosis and prognosis of CVD was reported in Morocco population (23). PAI was found to be a surrogate for sdLDL particles and negatively associated with LDL-C particle diameter. An increase in PAI indicates a reduction in the LDL particle diameter and a rise in the proportion of sdLDL. SdLDL particles are more prone to oxidation, to promote the formation of foam cells and LDL-C with oxidized apoprotein B is regarded as highly atherogenic characteristic. Furthermore, they can cause atherosclerosis by increasing lipid peroxidation, activating oxygen radicals, expressing adhesion molecules on endothelial cells which were linked to endothelial dysfunction (24). HDL-C lets the use of peripheral cholesterol by transporting it to the liver. Besides, it includes antioxidant enzymes such as paraoxonase (25).

There was no published study has yet examined the association between PAI and Raynaud's phenomenon. The data obtained in this sense is the first. In our study, we couldn't find any significant difference between PAI and Raynaud's phenomenon according to genders and RP patients group and control groups respectively ($p > 0.355$, $p > 0.875$). However PAI levels have showed that significant elevated between groups so It can be a simple, economic and non invasive marker to identify for future studies ($p < 0.000$). It may be used in clinical practice as several diseases

Limitations of the study

First, this study examined a small number of patients. As such, future studies should aim to test a larger population of patients. Retrospective study may have impeded clinical evaluation of patients with differences in culture, race, diet, lifestyle, demographic characteristics, laboratory tests and different postmenopausal and metabolic status could also affect PAI values. Besides, some pharmacological interventions such as hormone replacement therapy and vitamin D supplementation) could be considered, though most of them have yielded controversial outcomes. Most importantly, oral contraceptives, or medications known to affect lipid metabolism (lipid-lowering drugs, fish oil capsules, Beta-blockers, or diuretics) should be considered. Besides, the

retrospective nature of this paper is a limitation of its design.

Conclusions

In this study, we evaluated the role of PAI levels in RP patients and found no significant association for in the patient group. However, The levels of PAI between groups significant elevated between groups so It may be a good diagnostic candidate for diseases. We also suggest that multi-center and longitudinal studies are needed. **Funding**

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